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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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MEMORANDUM

SUBJECT: Linuron rebuttal comments for reproduction study; Caswell 528; EPA I.D. # 035506; Project 7-0130; Record No. 183739

TO: Michael McDavit, Review Manager
Special Review Branch (TS-767C)
and
Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division/HED (TS-769C)
James N. Rowe 12/5/86

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
12/5/86
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)
for CWF 12/12/86

ACTION: Review of rebuttal comments for linuron reproduction study; Caswell 528; EPA I.D. # 035506; Project 7-0130; Record No. 183739

RECOMMENDATIONS:

In light of the limited value of the histopathology data submitted in interpreting the reproductive study under consideration, and the additional concerns generated by the chronic and biochemical data concerning the overall reproductive toxicity of linuron, it is recommended that the study remain classified as Core supplementary and a repeat study be performed by the registrant.

1/3

INDUSTRY COMMENT:

In addition, the reviewer was unclear as to when the F_{1b} and F_{2b} rats began to receive linuron in the diet. Although the report states that rats were given the diets of their respective treatment groups at all times in the study, the reviewer noted that weanling weights (40-50 grams) were less than the body weights of the same rats (100-170 grams) started on test for the 90-day feeding portion of the study. The reviewer concluded that the rats "... were not started on linuron diets immediatedly at weaning." The reason for this apparent discrepancy in when weanlings were fed linuron is as follows: weanlings that were selected for the 90-day feeding studies were weighed at 21 days postpartum, fed their respective treatment group's diet, and held until all litters had been weaned. The official start of the 90-day feeding period was approximately one week after the last litter had been weaned. The official start was declared for record-keeping purposes and does not refer to when diets containing linuron were given to rats. By the start of the 90-day feeding portion of the study, the weanlings had gained 75-150 grams of body weight. At no time were the weanlings removed from their respective treatment group's diet.

EPA RESPONSE:

The EPA accepts this clarification of the apparent discrepancy noted for the weanling weights and the commencement of the dosing period.

INDUSTRY COMMENT:

The submission of histopathology data and the explanation of when the F_{1b} and F_{2b} were fed diets containing linuron should be sufficient to answer the questions raised in the Agency's rebuttal memo by Dr. Rowe. We, therefore, request a reconsideration of Dr. Rowe's recommendation for a repeat of this study and request upgrading of the study classification from Core supplementary to Core minimum.

EPA RESPONSE:

As discussed on the previous page, in light of the limited value of the histopathology data submitted in the interpretation of the reproductive study under consideration, and the additional concerns generated by the chronic and biochemical data concerning the overall reproductive toxicity of linuron, it is recommended that the study remain classified as Core supplementary and a repeat study be performed by the registrant.

DATA EVALUATION RECORD

INDUSTRY COMMENT:

The Agency's major concern with this study as stated in the subject J. Rowe letter (attached) is the lack of gross and histopathology data on the adults. The (A)gency considers these data essential to properly interpret the reproductive effects (decreased fertility and neonatal survivability) observed in this study.

In response to these concerns, histopathology data from rats used in the reproduction study were submitted to the Agency on October 6, 1896, as part of a larger overall in-depth study of the etiology of linuron-induced Leydig cell hyperplasia and adenoma formation. The study was entitled, "Biochemical and Pathological Effects of Linuron in Selected Tissues of Male and Female Rats." We refer the reviewer to these data.

Male and female F_{1b} and F_{2b} rats were retained from the reproduction study, were fed their respective diets containing 0, 25, 125 or 625 ppm linuron and were sacrificed at approximately 24 months of age. The purpose of retaining these rats was to confirm previous observations of endometrial hyperplasia and testicular adenomas noted in the final sacrifice of a two-year study with linuron. The gross and histopathology data from these rats is included in the aforementioned submission, i.e., "Biochemical and Pathological Effects of Linuron in Selected Tissues of Male and Female Rats" and should resolve concerns with the multigeneration reproduction study.

EPA RESPONSE:

While gross and histopathology data on F_{1b} and F_{2b} male and female groups were submitted by the registrant, the data are of limited value. Due to the additional tests performed, an inadequate number of animals were available for pathological examination (e.g., only 9-10 animals, male or female were available in the F_{1b} group and 6-15 males were available in the F_{2b} group) (see EPA review of aforementioned submission). At least twenty males and females are required in the 1982 EPA testing guidelines. Furthermore, the animals examined for pathological changes were kept for up to 2 years before sacrifice, sacrificed in extremis or found dead. In addition tissues of the epidymus, seminal vesicle and prostate were not evaluated as required in the guidelines. The EPA guidelines also require that males be sacrificed after the respective litter is sired and the females must be sacrificed after the pups are weaned. This allows for compound-related effects such as postimplantation losses (observable in the uterus) or testicular changes such as atrophy to be evaluated in an appropriate manner. Waiting until the end of two years or until death of the animals may obscure or eliminate many compound-related reproductive effects. Finally, the combined observations of interstitial cell adenomas and hyperplasia in the treated males and of cervical cystic hyperkeratosis and cystic endometrial hyperplasia in the treated females (effects observed in the two year chronic rat study; Kaplan, 1980), as well as the apparent ability of linuron to effect malerelated hormonal response, are indicators of reproductive toxicity in and of themselves. The observation of a dose-related increase in cystic endometrial hyperplasia and the possibilty that the NOEL for this effect is <25 ppm would further support the value of a new reproductive study.